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RESEARCH ARTICLE

lncRNA PVT1 Expression in Cervical Cancer: Association with HPV Status, Lymph Node Involvement, and Treatment Response

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Abstract

Introduction: Cervical cancer accounts to about 25-30% of malignancy seen in females in South India. The age-standardized incidence rate of cervical cancer in South India is 22.1%. It is commonly associated with Human Papilloma Virus (HPV -16, HPV-18) infection and most cases are found to present with advanced staging of cancer. The increased number of cases is due to poor access for cervical cancer screening and barriers due to socio-economic status. The role of long noncoding RNA plasmacytoma variant translocation 1 (lncRNA PVT1) in cervical cancer has not been explored in cervical cancer though it has been associated with other types of cancer. The aim of this study is to evaluate the expression of lncRNA PVT and its association with HPV status, lymph node metastasis and response to therapy. **Materials and Methods:** A prospective study was conducted for a duration of 12 months in radiation oncology outpatients. Paired cervical biopsies were taken from 80 newly diagnosed cervical cancer patients. HPV DNA and PVT1 expression was analysed using multiplex PCR and Rt-qPCR respectively. Statistical tests were used to analyse the correlation between lncRNA PVT-1 expression and clinicopathological characteristics, HPV status, lymph node metastasis and response to therapy. **Results:** Among 80 patients, 63 (78.75%) had squamous cell carcinoma and 17 (21.25%) had adenocarcinoma; 62.5% presented at FIGO stage IIIB. HPV infection was detected in 64 cases (80%), and lymph node metastasis in 16 (20%). All tumours measured ≥4 cm. After 12 weeks of treatment, 63 patients (78.75%) achieved complete response. Elevated PVT1 expression correlated with tumour size, HPV status, lymph node metastasis, and partial treatment response. ROC analysis showed an AUC of 0.525 for lymph node metastasis and 0.718 for predicting partial response. **Conclusion:** PVT1 expression demonstrates a significant association with major clinicopathological factors in cervical cancer. However, it does not possess predictive value for lymph node metastasis. Given its discriminatory capacity, PVT1 may serve as a biomarker for therapeutic response and could thus be valuable for stratifying treatment outcomes.

Keywords: lncRNA PVT1- cervical cancer- Human papilloma virus- lymph node metastasis- treatment response- biomarker

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Introduction

Cervical cancer is the fourth most common cancer seen in women across the world, with 662,044 new cases and 348,709 deaths reported in 2022 [1]. The burden of this disease is particularly pronounced in low- and middle-income countries, with India accounting for 19% (127,526 cases) of new diagnoses and 23% (79,906 deaths) of global mortalities that year [2, 3]. Cervical cancer accounts to the second commonest cancer among women in India with an incidence rate of 18.3 per 100,000 women and a mortality rate of 11.2 per 100,000 which is more than the average mortality rate of 7.1 per 100,000 [4]. This incidence is notably higher in South India,

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where rates range from 15 to 22.1 per 100,000 women, and cervical cancer constitutes 25–30% of all female malignancies in the region [5].

Furthermore, approximately 60% of patients with cervical cancer are diagnosed at advanced stages, specifically FIGO IIB–IV, resulting in a survival rate between 48.7% and 51.7% [6]. The primary etiological factors for cervical cancer are infections with HPV-16 (55–67%) and HPV-18 (13–19%) [7]. Persistent infection with these human papillomavirus types induces genomic instability within host cells and disrupts regulation of cellular pathways [8]. In patients with cervical cancer, variations in disease progression, therapeutic response, and clinical outcomes underscore the pressing need to identify new molecular biomarkers. These biomarkers, used in conjunction with established prognostic indicators, have the potential to form personalized treatment strategies for cervical cancer.

Long non-coding RNAs (lncRNAs), consists of more than 200 nucleotides, play significant roles in oncogenesis through the regulation of gene expression and cellular processes. Among these, plasmacytoma variant translocation 1 (PVT1), located on chromosomal region 8q24 near the MYC oncogene, has been implicated in several malignancies, including breast, pulmonary, gastric, and colorectal cancers [9]. PVT1 functions by stabilizing the MYC protein, modulating critical pathways such as Wnt/β-catenin, PI3K/AKT, and MAPK/ERK, and acting as a competing endogenous RNA (ceRNA). Upregulation of PVT1 correlates with increased proliferation, invasion, metastasis, chemoresistance, and poor prognosis in various cancers [10, 11]. However, the potential of PVT1 as a biomarker, and its association with clinicopathological features in the South Indian population, remain unexplored. To date, no molecular studies have investigated PVT1 lncRNA in cervical cancer patients from South India, despite the high prevalence of the disease in this region. Assessing the association between PVT1 lncRNA expression and prognostic factors such as HPV status, lymph node involvement, tumour size, and treatment response is essential for developing region-specific risk stratification models and informing targeted surveillance and interventions. This study seeks to determine the association of PVT-1 lncRNA with HPV status and its potential of PVT-1 lncRNA as a biomarker for predicting lymph node metastasis, and therapeutic response in patients with cervical cancer.

Materials and Methods

A prospective study was conducted over a period of one year, from September 2024 to August 2025, at the Cancer Institute (WIA) and SRM Medical College Hospital and Research Centre. It was a time-bound study that included newly diagnosed cervical cancer patients, while patients who were already undergoing radiotherapy or chemotherapy were excluded. A total of 230 patients were screened for cervical cancer using Pap smear, visual inspection with 4% acetic acid, and clinical examination. Among the screened patients, 194 cases were diagnosed with cervical cancer, of which 80 cases met the inclusion criteria for this study. Histopathological diagnosis of cervical cancer (SCC vs. adenocarcinoma) was confirmed by a senior pathologist. Adjacent normal tissue was defined as cervical epithelium taken >2 cm from the tumor edge and confirmed to be histologically normal. Staging of cervical cancer was performed according to the FIGO 2018 Classification (International Federation of Gynaecology and Obstetrics). The study was approved by the ethics committees of both institutions (8505/IEC/2023, IEC/2024/August 1).

Identification of Human Papilloma Virus Infection (HPV):

HPV infection was identified using multiplex polymerase chain reaction with reagents from HiMedia Laboratories Pvt Ltd [12] to identify HPV-16 and HPV-18. The protocol of the kit is as shown in the Table 1,

The dyes utilized for internal control, HPV-16, and HPV-18 are FAM, Texas Red, and Cy5, respectively. HPV PCR results were deemed positive when the cycle threshold value was ≤38, with a detection limit of approximately 10 copies per reaction. The kit demonstrates a specificity of 100%.

Fluorophores FAM, Texas Red, and Cy5 were utilized for the detection of HPV-16, HPV-18, and the internal control, respectively. Samples yielding a cycle threshold value of ≤38 were considered positive for HPV PCR. The assay demonstrates 100% specificity for the identification of HPV-16 and HPV-18 infections, with a limit of detection of approximately 10 copies per reaction.

Identification of PVT-1 lncRNA from cervical biopsy

Samples of both cancerous tissue and adjacent normal tissue (paired cervical biopsy) were collected and preserved in an RNA stabilising solution (Sisco Research Laboratories Limited) using Eppendorf tubes, which were then stored at -80°C.

RNA Extraction

The HiPurA Tissue RNA Purification Kit [13] was used for RNA extraction following the manufacturer's guidelines. The purity of the extracted RNA was evaluated by spectrophotometry, with an A260/A280 ratio between 1.8 and 2.0 indicating high purity.

Synthesis of cDNA (complementary DNA) and quantitative PCR (qPCR)

The PrimeScript One Step RT-PCR Kit (TaKaRa) [14] was utilized to convert extracted RNA into cDNA through reverse transcription. For LncRNA PVT-1, the melting temperature is 60°C, using the forward primer 5'-CCGACTCTTCCTGGTGAAGC-3' and the reverse primer 5'-GTATGGTCAGCTCAAGCCCA-3'. U6 small nuclear RNA was used as the internal control. The qPCR protocol began with an initial denaturation at 95°C for five minutes, followed by cycles of denaturation at 95°C for forty-five seconds, annealing at 55°C for forty-five seconds, elongation at 72°C for sixty seconds, and concluded with a final elongation step lasting fifteen minutes at 72°C. RT-qPCR was carried out on the ALTA

48 Real-Time PCR System (AltemisLab, India). Relative gene expression was quantified using the $2^{\Delta\Delta CT}$ method, and all qPCR reactions were performed in triplicate to ensure data reliability.

Treatment Details and Its Response

Patients received external radiation totalling 50.4 Gy, administered as 1.8 Gy per fraction across five fractions per week over 28 sessions, along with weekly cisplatin at a dose of 40 mg/m². This was followed by three sessions of high-dose-rate (HDR) brachytherapy, delivering a cumulative dose of 21 Gy to point A. Adjustments to the total external radiation and intracavitary doses were made based on the feasibility of intracavitary application. A nodal boost of 5 Gy was provided for patients with enlarged pelvic nodes. Following 12 weeks of therapy, patient response was evaluated through clinical examination in accordance with the World Health Organization risk criteria for solid tumours.

Research Hypothesis

Overexpression of lncRNA PVT-1 is associated with high-risk HPV types (HPV-16 and HPV-18) related cervical cancer, increased likelihood of lymph node metastasis and a poor clinical response to chemoradiotherapy.

Statistical Plan for Analysis

The data will be analysed using Graphpad 7.0 and IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test and Mann-Whitney test will be used to analyse the statistical significance of the results. Statistical significance is defined as a p value less than 0.05. The potential of PVT-1 lncRNA as a biomarker for lymph node metastasis and treatment response will be evaluated through receiver operating characteristic (ROC) analysis. Multivariate logistic regression analysis will be performed to analyse the utility of lncRNA PVT-1 as an independent predictor of partial treatment response.

Results

Of the 80 patients newly diagnosed with cervical cancer, the mean age was 57.4 years (SD = 6.9 years), with the majority belonging to the 51–60 year age group (39 patients, 48.75%) and 13 patients (16.25%) in the 41–50 year group. Most participants were postmenopausal (58, 72.5%) and married (61, 76.25%). The majority had attained only primary education or less (61, 76.25%), and most were housewives (56, 70%). Urban residency was common (52, 65%), and none of the patients had received HPV vaccination. Histopathological analysis revealed that squamous cell carcinoma (SCC) was predominant [63 (78.75%)], while adenocarcinoma (ADC) was observed in 17 (21.25%) (Table 2).

Table 1. PCR Protocol of Human Papilloma Virus (HPV) Multiplex PCR

Initial Denaturation	95°C for 10 minutes
Denaturation	95°C for 15 seconds (40 cycles)
Annealing	55°C for 20 seconds

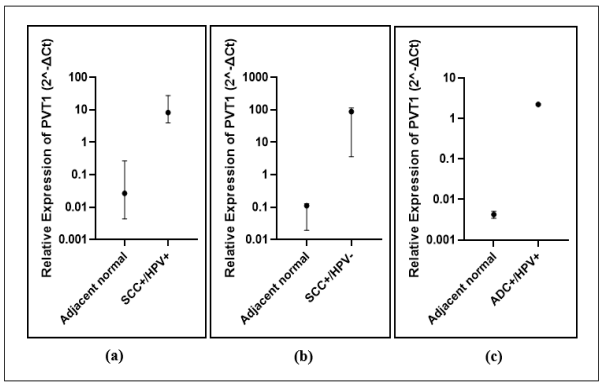

Figure 1 (a), (b), and (c). Depict the Relative Expression Levels of lncRNA PVT1 ($2^{-\Delta Ct}$) in Adjacent Normal Cervical Tissues Versus Cervical Cancer Tissues, Further Stratified by Histological Subtype and HPV Status. Data are presented as medians with interquartile ranges, and statistical significance was assessed using the Mann–Whitney U test ($p < 0.05$)

Figure 1 (a),1 (b),1 (c) demonstrates that PVT1 expression is elevated in cervical cancer tissues, especially in HPV positive squamous cell carcinoma, compared to adjacent normal tissues. This suggests that PVT1 overexpression is associated with malignant transformation, particularly in the presence of high-risk HPV infection. The Mann–Whitney U test showed significantly higher PVT1 expression in SCC (HPV+ and HPV−) and ADC (HPV+) groups compared to adjacent normal controls ($p < 0.05$).

PVT 1 expression across the various histological type of cancers and its correlation with HPV status and lymph node metastasis was analysed (Figure 2 (a)). PVT 1 expression was seen highest in the HPV+/SCC+/LN- subgroup. Fisher's exact test revealed a significant link between lymph node metastasis, cancer histology, and HPV status ($p \approx 0.0005$). The ADC subgroup showed no lymph node metastasis. ROC analysis of PVT-1 yielded an AUC of 0.525 (95% CI: 0.3702–0.6798; $p = 0.8343$), indicating no discriminative value for lymph node metastasis (Figure 2 (b)).

In this study, 78.75% (63/80) had a complete response to therapy, while 21.25% (17/80) showed a partial response. Figure 3 (a) demonstrates the PVT-1 expression in association with clinical response to therapy. ANOVA analysis showed an overall difference in PVT1 expression between the various subgroups of histological types of cancer, HPV status, treatment response. Tukey's multiple comparison test identified that SCC+/HPV+ with partial response had a statistically significant higher expression than SCC+/HPV+ with complete response ($p<0.0001$). No significant association was seen between the SCC+/HPV+/CR and ADC+/HPV+/CR group($p=0.08$) nor between the PR vs.CR comparisons within the ADC groups. This shows that increased expression of PVT-1 is associated with partial treatment response within the HPV positive SCC group of patients while this trend is not seen in the ADC group of patients.

PVT-1 lncRNA can be used to differentiate the two clinical outcomes of therapy, partial and complete

Table 2. Clinicopathological Features of Cervical Cancer Cases (N=80)

Demographic characteristics	Number (%)
1. Age	
41-50	13 (16.25)
51-60	39 (48.75)
61-70	28 (35)
2. Marital Status	
Married	61 (76.25)
Unmarried	19 (23.75)
Divorced/Separated	0 (0)
3. Menopausal status	
Premenopausal	22 (27.5)
Postmenopausal	58 (72.5)
4. Education	
Primary Education and below	61 (76.25)
Secondary Education	19 (23.75)
College and above	0 (0)
5. Occupation	
Housewife	56 (70)
Employee	16 (20)
Farmer	8 (10)
Business	0 (0)
Other	0 (0)
6. Residence	
Rural	28 (35)
Urban	52 (65)
7. History of HPV Vaccination	
Yes	0 (0)
No	80 (100)
8. Type of cervical cancer	
Squamous cell carcinoma	63 (78.75)
Adenocarcinoma	17 (21.25)
9. FIGO Staging	
IB3	9 (11.25)
IIIB	50 (62.5)
IIIC1	16 (20)
IVA	5 (6.25)
10. Human Papilloma Virus (HPV) Status	
HPV positive	64 (80)
HPV negative	16 (20)

treatment response. ROC analysis revealed a moderate diagnostic performance of the PVT-1lncRNA to differentiate the clinical outcomes of therapy with an AUC curve of 0.718 with a p value of 0.006 (Figure 3 (b)). A multivariate logistic regression analysis was conducted to identify independent predictors of partial treatment response at 12 weeks. After adjusting for FIGO stage and histological subtype of cervical cancer, LncRNA PVT-1 was not found to be an independent predictor of partial treatment response (adjusted OR: 0.98; 95% CI: 0.86–1.10).

Discussion

Demographic Characteristics of Study Patients

The patient demographics in this study align with global cervical cancer trends, except for minor regional differences. The average patient age was 57.4 years (SD = 6.9), with most cases occurring in the 51-60 year group (48.75%), mirroring findings that late diagnosis is common in low and middle income countries due to limited screening access [15]. Most participants were married women (76.25%), differing from Western studies where more patients are unmarried; these studies also report a 63% higher chance of late diagnosis and poorer outcomes for unmarried women [16].

In the study population, 72.5% were postmenopausal women, suggesting suboptimal cervical cancer screening during their reproductive years [17]. Limited access to education and lower socio-economic status may serve as barriers to healthcare, potentially contributing to the higher incidence of cervical cancer observed in this group, consistent with findings from previous studies [18]. Additionally, 70% of participants were housewives, which could account for reduced health seeking behaviours due to economic dependency, likely resulting in lower rates of cervical cancer screening and advanced stage diagnoses within this demographic [19]. The urban predominance of 65% among study participants is attributable to referral bias associated with the study location, despite similar or potentially lower disease burden in rural populations.

This study found no HPV vaccination, reflecting trends in low- and middle-income countries, unlike the higher rates in high income nations. As of 2023, HPV vaccine coverage for the first dose was 27%, and only 20% received the full course among children aged 9-14 [20]. In low-income countries, less than a quarter receive the vaccine even though these regions bear 84–90% of the global cervical cancer burden [21, 22]. Modelling studies project that without active vaccination programs, there could be an additional 44.4 million cervical cancer cases worldwide by 2069, with two-thirds expected in countries with lower development indexes [23]. The results underscore the critical importance of intensifying initiatives aligned with the WHO Global Strategy for cervical cancer elimination, which aims to achieve 90% HPV vaccination coverage by age 15, 70% screening, and 90% access to treatment by 2030 [24]. Squamous cell carcinoma (78.75%) was the predominant histopathological type of cancer in the study. This is similar to the global patterns where SCC forms 70-80% cervical cancer [25].

In this study, Stage IIIB (62.5%) was seen in majority followed by IIIC1 (20%), IB3 (11.25%) and IVA (6.25%) which is represents a significantly skewed distribution towards a locally advanced cervical cancer($p<0.001$). This is similar to previous studies done in India and other lower- and middle-income countries where about 60-70% patients present with advanced stages of the disease. This may be due to delay in screening, delayed recognition of symptoms and barriers in referral [26]. Previous studies have mentioned that after applying FIGO 2018

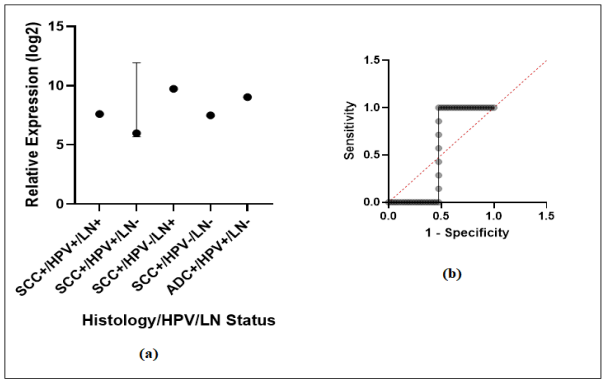

Figure 2. (a). Relative PVT1 Expression Across Histology–HPV–lymph Node Subgroups, Shown as Median with Interquartile Range; Statistical Analysis Performed Using Fisher's Exact Test ($p \approx 0.0005$). (b). Receiver operating characteristic (ROC) curve evaluating the ability of PVT1 expression to predict lymph-node metastasis in cervical cancer (AUC of 0.525; $p = 0.8343$).

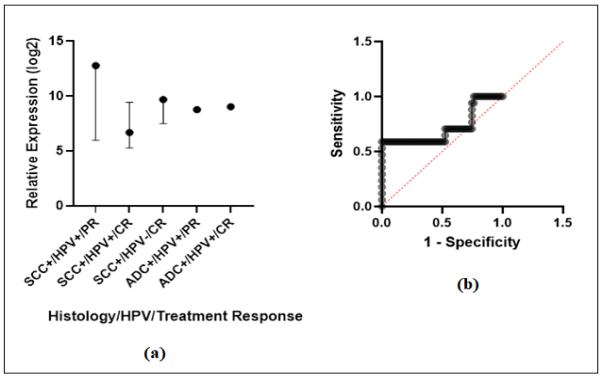

Figure 3. (a). Relative Expression of lncRNA PVT-1 among Histology–HPV–treatment-response Subgroups Expressed as Median and Interquartile Range; Statistical Analysis Performed Using ANOVA ($p<0.0001$). (b). Receiver operating characteristic (ROC) curve evaluating the ability of PVT1 lncRNA to predict treatment response in cervical cancer (AUC curve of 0.718 with a p value of 0.006).

staging, IIIC1 is the most frequent stage mainly due to improved assessment of lymph nodes (35-45%) [27, 28]. The reduced number of IIIC1 in this study may be due to referral bias towards clinically obvious parametrial disease which is typical of radiation oncology cohorts. Stage IVA comprises 6.25% of study patients in this study which documents the late presentation with adjacent organ involvement which is similar to studies from high burden settings [26, 29].

PVT1 Expression in Cervical Cancer Tissues

PVT-1 expression is elevated in cervical cancer tissues, particularly in HPV positive squamous cell carcinoma, compared to normal tissues. Iden et al. reported similar results, noting increased levels of PVT-1 lncRNA in cancerous tissues versus normal ones in a study of 121 invasive cervical carcinoma cases [30]. Additionally, Wang et al. discovered elevated PVT-1 lncRNA in both HPV-positive and HPV-negative squamous cell carcinoma tissues, suggesting its potential as a biomarker [31]. There are multifactorial reasons behind the mechanism of PVT -1 overexpression in cervical cancer. PVT-1 represents a frequent site of HPV integration in cervical cancer which suggests a direct relationship between viral infection and PVT-1 dysregulation. Previous studies reveal that knockdown of PVT-1 results in decrease in proliferation, migration and invasion of cervical cancer. It can also lead to increase in apoptosis and sensitivity to cisplatin [30].

PVT 1 Expression and HPV Status

This study found that PVT-1 expression was highest in HPV-positive squamous cell carcinoma, with varying levels seen in other cancer histological types. In contrast, Wang et al. reported no difference in PVT-1 expression between HPV-positive and HPV-negative individuals [31]. Additionally, this research showed that PVT-1 levels increased with tumour size and were higher in cancer patients than in healthy controls. The study involved 156 participants: 135 (86.5%) were HPV positive and 21 (13.5%) were HPV negative. It also revealed that PVT-1 inhibits TGF-β, contributing to cervical cancer development. Iden et al mentioned that hypoxic conditions and stimulation of immune response with interferon alpha increases the expression of PVT-1 [30].

PVT-1 and Lymph Node Metastasis

This study observed that PVT-1 expression was highest in the HPV-positive, SCC-positive, lymph node-negative subgroup. ROC analysis showed an area under the curve (AUC) of 0.525 and a p-value of 0.83, indicating that PVT-1 is not a suitable biomarker for lymph node metastasis, contrary to findings reported in earlier research [32]. For instance, Qin et al. observed elevated PVT-1 expression in patients with head and neck squamous cell carcinoma exhibiting lymph node metastasis, relative to those without such involvement [33]. Variations between our results and prior studies may be explained by tumour heterogeneity and differences in the study populations.

PVT-1 and Treatment Response

The relationship between PVT-1 expression and treatment response is one of the most important findings in this study. ANOVA analysis identified that SCC+/HPV+ patients with partial response to treatment had statistically significant higher PVT-1 expression than those patients with complete response to treatment. ROC analysis with an AUC of 0.718($p=0.006$) showed a moderate diagnostic performance for PVT-1 in differentiating partial and complete treatment response. Gao et al documented increased cytotoxicity to cisplatin compared to control cells on knocking down the PVT-1 in cervical cancer cells. This shows its role in chemoresistance. PVT-1 due to its association with nucleolin, a multifunctional stress responsive protein can facilitate resistance due to therapeutic stress.

Yao et al. found that PVT-1 contributes to chemoresistance by influencing apoptosis, hypoxia, autophagy, epithelial-mesenchymal transition, and DNA damage repair. As a ceRNA, PVT-1 promotes cervical cancer proliferation, migration, and invasion, potentially

leading to chemoresistance. This study shows elevated PVT-1 expression in HPV-positive SCC patients with partial response, but not in adenocarcinoma patients, suggesting resistance related to cancer histology[34]. These findings may reflect unique molecular pathways and PVT-1 interactions with HPV oncoproteins across cervical cancer subtypes.

Clinical Implications and Future Directions of PVT-1

The findings of this study indicate that PVT-1 has potential as a diagnostic marker for distinguishing cervical cancer patients from healthy individuals. LncRNA PVT-1 overexpression may serve as a predictor of treatment response, particularly among patients who are at risk for showing a partial response to chemoradiation. Stratifying patients according to lncRNA PVT-1 expression could facilitate the identification of individuals who require closer surveillance within therapeutic strategies.

Limitations and Considerations

The findings of this study cannot be extrapolated to all patients with cervical cancer due to the limited sample size and should be validated in larger, independent, multicentric cohorts with longitudinal follow-up and analysis of survival endpoints. Furthermore, investigation of the molecular mechanisms underlying the elevated expression of PVT-1 lncRNA in patients exhibiting a partial response to therapy is essential for understanding the biological factors driving therapeutic resistance.

In conclusion, this study underscores the importance of evaluating PVT-1 lncRNA expression in cervical cancer. Results indicate overexpression of the lncRNA, especially in HPV-positive squamous cell carcinoma. Although PVT-1 lncRNA does not serve as a discriminative biomarker for lymph node metastasis, it is significantly linked to treatment response and plays a role in chemoradioresistance, suggesting its potential as a predictor for treatment response stratification. Further research is required to assess its efficacy in identifying patients who exhibit suboptimal responses to cancer therapy and to elucidate the molecular mechanisms underlying therapeutic resistance.

Declarations

Funding

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Clinical trial registration

Not applicable

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

The custom code was used.

Authors' contributions

Anusha Gopinathan, Leela Kakithakara Vajravelu and Ram Madhavan contributed to the conception, design, and final drafting of the manuscript. Gopika Rajeev and Ram Madhavan contributed to data collection. Anusha Gopinathan, Gopika Rajeev, Ram Madhavan contributed to the primary drafting of the manuscript. Leela Kakithakara Vajravelu supervised the study. All authors approved the final version for submission.

Ethics approval

This study was approved by Ethics Committee of the Cancer Institute (WIA), Chennai and SRM Medical College Hospital and Research Centre.

Consent to participate

Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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